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Behavioral and genetic characterization of contextual fear conditioning and related phenotypes using the BxD RI panel

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Contextual fear conditioning is a form of Pavlovian fear conditioning, during which an organism learns to fear a previously neutral stimulus assembly (context) following its close temporal presentation with an aversive stimulus. In mouse models, freezing behavior is typically used to quantify learned fear response in fear conditioning paradigms. Several underlying phenotypes may impact freezing to context following conditioning, including fear/anxiety, hippocampus-dependent learning, non-hippocampus dependent learning, and locomotion. To better understand latent constructs impacting performance in contextual fear conditioning and correlated behaviors, we tested 4 BXD RI strains previously found to show extreme contextual fear conditioning phenotypes (highest/lowest freezing among 31 strains) and intermediate freezing BXD parental strains, C57BL/6J and DBA/2J, in a battery including locomotor, anxiety, contextual/cued fear conditioning and non-associative hippocampus-dependent learning behaviors. Hippocampi were dissected at the conclusion of the battery, and expression of two candidate genes (identified using QTL mapping in a larger nicotine withdrawal project) for contextual fear conditioning was quantified using qPCR. Resulting behavioral and gene expression data were analyzed using an exploratory factor analysis, which extracted five unique latent constructs (factors). The top extracted factor represented a combined locomotor/exploration/anxiety phenotype, while other factors appeared to represent unique variation in locomotion and anxiety. Candidate gene expression and fear conditioning performance differentially segregated into one factor representing performance in the post-shock phase of training and another representing performance in contextual and cued testing. These findings suggest inextricable interactions between commonly studied mouse phenotypes and point to potential gene candidates for different phases of fear conditioning.